

Is There a Relationship Between Disease Control and Liver Function in Children with JIA Receiving Treatment with Methotrexate?

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Abstract

Juvenile Idiopathic Arthritis (JIA) is one of the commonest chronic diseases of childhood. Despite significant advances in the field of biologics offering a much wider a range of treatment options, Methotrexate remains the 1st line disease modifying drug [1] especially for those with polyarticular disease or associated uveitis. Response to methotrexate is variable and though work is ongoing to try and predict those who will respond well, this has not yet translated into clinical practice. Methotrexate can be associated with significant side effects [2,3] and adherence can be challenging. Currently assessment of adherence in the patient with apparently resistant disease relies on patient or parent reporting, which may not always be accurate.

Liver function is routinely monitored in children and young people (CYP) on Methotrexate to look for evidence of liver toxicity [4-6]. It is not uncommon for transaminases to be abnormal while taking methotrexate [7]. A perceived relationship between normal liver function and methotrexate adherence has been reported by some practitioners [8].

Keywords Juvenile idiopathic arthritis; Methotrexate; Liver; Rheumatology; Physiotherapy

Aim

Our aim was to evaluate the relationship between liver function and disease control in CYP with JIA being treated with methotrexate. Specifically, we wanted to evaluate whether those with "low-normal" liver function had evidence of poorer disease control.

Methods

All CYP aged 0-18 currently being treated with methotrexate by the Rheumatology Team at Nottingham Children's Hospital (NCH) were identified via the nursing database. CYP with a non-Juvenile Idiopathic Arthritis diagnosis or systemic JIA were excluded. At NCH blood monitoring tests are taken at the time of clinic appointments, so therefore we anticipated that most blood test results could be linked to a corresponding episode of clinical care. Also all monitoring blood tests take place at the hospital and therefore blood tests results would be available on the hospital computer system. The study did not include CYP whose care was being delivered by outreach services as their methotrexate monitoring is managed by their local team.

All ALT results available for eligible patients were identified from the hospital computer blood results system from 1/11/2013 to 31/10/2014. ALT results are reported as Units/Litre and were categorised into ≤ 10 , 11-15, 16-45 and >45 . These categories were chosen because we specifically wanted to look at the relationship between disease control and "low-normal" liver function. Due to the low number of ALT results ≤ 10 , clinical data was collected for corresponding episodes of clinical care for all of these results. For all the other categories of ALT a random number generator was used to select those results for which further data would be collected. Clinical

data was collected retrospectively from clinical records; clinical episodes within 2 weeks of the blood test were used to correspond with an ALT result. Clinical data was extracted from computerized hospital letters, patient notes and physiotherapy records. Data was collected for all of the variables included in the JADAS score and documentation of adherence to methotrexate therapy.

Results

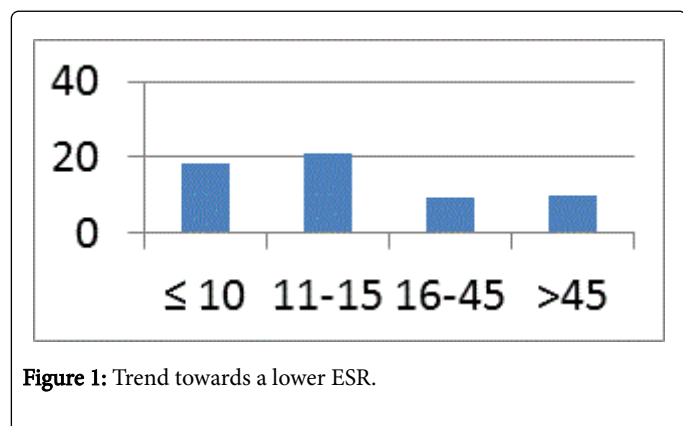
There were 20 episodes of ALT ≤ 10 in 15 different patients, 71 ALTs 11-15 in 33 patients, 146 16-45 in 70 patients 75 >45 in 34 patients. Data was collected for 20 episodes ≤ 10 , 21 of 10-15, 23 of 16-45 and 24 of >45 . Due to the retrospective nature of the data collection there was insufficient data available to analyze further the full components of the JADAS score, so hereafter we only looked at the active joint count and ESR. Once hospital records were looked at 3 further exclusions were made (Table 1).

ALT	≤ 10	11-15	16-45	>45
Number of results	20	21	23	24
Number of patients	15	19	19	20
Further exclusions	2 (Not yet started MTX)	0	1 (JDM overlap)	0
Analysed results/ number of pt	18/14	21/19	22/18	24/20
Active joint count documented	14	16	20	22
ESR available	14	20	24	23

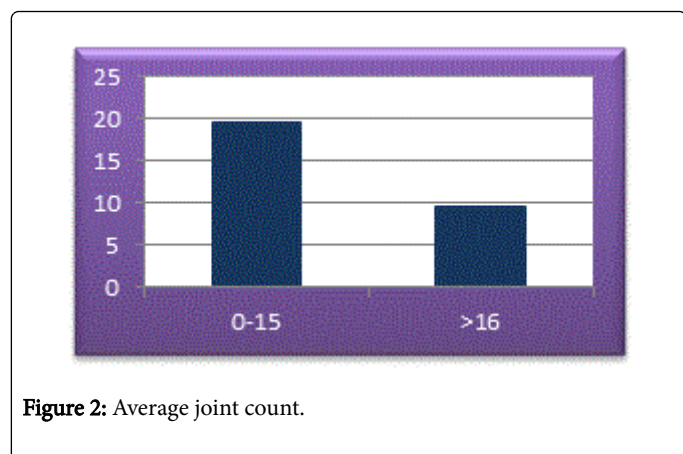
Table 1: Baseline data.

ESR

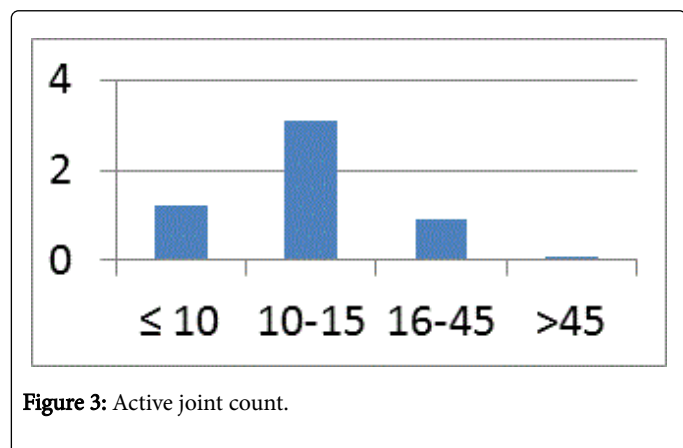
A trend towards a lower ESR was noted in those episodes of care corresponding to higher ALTs, but this did not reach statistical significance (Figure 1).



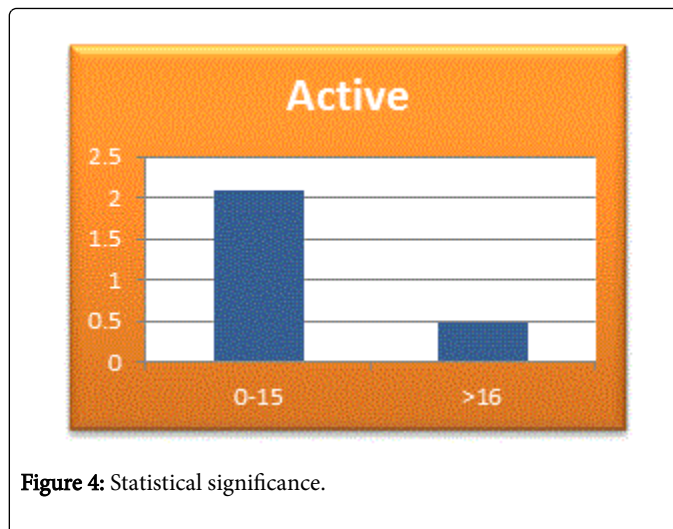
When the groups were combined into ALT ≤ 15 and ALT >15 then a significant difference was seen between the 2 groups in terms of ESR (p=0.001) using the unpaired students T-test (Figure 2).



The active joint count in those episodes of care associated with ALT >45 was lower than those with lower ALTs (Figure 3).



Once combined the trend was clearer and reached statistical significance using the unpaired students t-test (p=0.0174) (Figure 4).



Conclusions

This is a small study. The data was retrospectively collected and consequently data was insufficient to analyze against validated composite measures of disease control. We did not look at other markers which could influence disease activity or the hepatic effects of methotrexate, such as use of additional drugs. It is likely that a number of patients will have been taking Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), specifically Ibuprofen. However, given the apparent increase in the disease activity level in those with “low-normal” ALT, we would anticipate higher use of NSAIDs in this group for symptomatic relief, so we feel it is unlikely to introduce a bias into the results. This would however require further exploration in more detailed studies. It should also be noted, that although NSAIDs have hepatic dysfunction as a recognized side-effect, no association has been made between NSAID use and hepatotoxicity on methotrexate in JIA.

Despite some limitations, we believe this data does demonstrate a potentially interesting phenomenon in a significant difference in disease control between those with “low normal” ALTs and those with “high normal or abnormal” ALTs in 2 of the components of the JADAS score. This effect is observed despite the fact that those with abnormal LFTs are more likely to have had deliberate missed doses of methotrexate due to abnormal liver function, or intercurrent infections causing abnormal liver function.

Previous studies have reported variations in liver toxicity with different genetic polymorphisms involved in methotrexate metabolism, and in cellular methotrexate polyglutamate patterns [9,10]. These have exciting potential to help us predict who is likely to develop toxicity related to methotrexate and to tailor treatment to individual genetic makeup. Polymorphisms which may predict disease control have not correlated with those which may predict toxicity, and the same is true for those studies looking at polyglutamate patterns [9,10]. This project aimed to ask a slightly different question having looked specifically to see if those with “low-normal” liver function on methotrexate have poorer disease control. We believe this is the first study to report such an association. There was insufficient data to assess drug adherence and it is impossible to say from the data whether the observed effect is a consequence of adherence or individual variation in metabolism of methotrexate. If this result is a function of poor adherence rather than

individual response to methotrexate, then this may go some way to explaining the lack of association between hepatic toxicity and efficacy in previous studies. We would not advocate the use of ALT as a marker of response to treatment or adherence based purely upon this data. This does however potentially represent a cheap and readily available method of assessing either adherence, or the individual response to methotrexate and therefore warrants further investigation in a more robust study.

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